ANALYSIS OF PATHOLOGICAL RESPONSE AFTER NEOADJUVANT CHEMORADIATION IN STAGE III BREAST CANCER

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CERTIFICATE

I hereby certify that this dissertation on **"Analysis of pathological response after neoadjuvant chemoradiation in Stage III Breast Cancer"** is a bonafide work done by **Dr.M.SIVAKUMAR,** in the Department of Surgical Oncology, College of Oncological sciences, Cancer Institute (WIA), Chennai, under my guidance and supervision, to my satisfaction.

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CERTIFICATE

This is to certify that the dissertation entitled "**Analysis of pathological response after neoadjuvant chemoradiation in Stage III Breast Cancer**" is a bonafide work done by **Dr. M.SIVAKUMAR** in the Department of Surgical Oncology, College of Oncological sciences, Cancer Institute (WIA), Chennai in partial fulfillment of the University rules and regulations for award of MCh surgical oncology under my guidance and supervision during the academic year 2011 to 2014.

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BACKGROUND

Locally advanced Breast cancer (LABC) is a heterogenous group of tumor with marked variation in outcome and high propensity for local, regional and distant failure. Hence integrated multimodality approach had become standard for optimal patient outcome. Neoadjuvant chemotherapy had evolved as the conventional and standard of care in treatment of LABC. Neoadjuvant chemoradiation is also a safe and valid multimodality treatment option for LABC.[1,2,3,4]

Preoperative chemotherapy is established as standard treatment for LABC with varying pathological response rate.[5] There is significant association between the extent of pathological response and longterm outcome in terms of disease free survival- DFS and overall survival-OS.[6] Preoperative chemoradiation is associated with higher pathological response rate that translate in terms of survival benefit.

Shanta V, et al analysed one of the largest database containing 1,117 LABC patients treated with preoperative concurrent chemoradiation during 1990 to 1999. The reported clinical response rate

was 91 % and complete pathological response rate up to 33.7 %.

CONTENTS

1.AIMS

1. To analyse the pathological response rate following neoadjuvant chemoradiation in stage III breast cancer.

2. To study the outcomes in terms of disease free survival and overall survival.

3. To determine the clinicopathological factors associated with pathological response and survival outcomes.

2.BACKGROUND

Locally advanced Breast cancer (LABC) is a heterogenous group of tumors with marked variation in outcome and high propensity for local, regional and distant failure. Hence integrated multimodality approach had become standard for optimal patient outcome. Neoadjuvant chemotherapy has evolved as the conventional and standard of care in treatment of LABC. Neoadjuvant chemoradiation is also a safe and valid multimodality treatment option for LABC.[1,2,3,4]

Neoadjuvant chemotherapy is established as standard treatment for LABC with varying pathological response rate.[5] There is significant association between the extent of pathological response and longterm outcome in terms of disease free survival- DFS and overall survival-OS.[6] Neoadjuvant chemoradiation is associated with higher pathological response rate that translate in terms of survival benefit.

Shanta V, et al analysed one of the largest database containing 1,117 LABC patients treated with neoadjuvant concurrent chemoradiation during 1990 to 1999. The reported clinical response rate was 91 % and complete pathological response rate up to 33.7 %. Patients with complete pathological response rate had long term survival. The DFS at 5, 10 and 15 years was 76.6%,69.6% and 63.6%

respectively. The corresponding overall survival was 86.5%, 78% and 76.2%.[7]

Formenti et al reported 44 patients treated with neoadjuvant twice weekly paclitaxel and concurrent radiotherapy had pathological response rate of 34% in the mastectomy specimen and 16% complete pathological response rate (clearance of invasive cancer in both breast and axilla) that translate in to better survival outcomes.[8]

Neoadjuvant concurrent chemoradiation for LABC was associated with acceptable morbidity and mortality.[9] The most common toxicity reported was skin related toxicity.[9,10]

Ipsilateral involvement of supraclavicular node was considered as a poor sign with high risk of distant metastasis. Majority of them developed distant metastasis within 1 year and cure was rare. But with aggressive combined modality treatment , the outlook of these patients once considered metastatic stage IV disease with dismal outcomes had changed with longterm disease free and overall survival. Brito et al reviewed three prospective trials of combined-modality therapy for locally advanced breast cancer treated at M.D. Anderson Cancer Center between 1974 and 1991. Seventy patients with ipsilateral supraclavicular metastases with no evidence of other distant metastases were identified

and analysed. With median follow up of 11.6 years, the results were equivalent to stage III B disease but better than stage IV patients, in terms of local control rate and survival (DFS and OS). They strongly recommend aggressive combined modality treatment for LABC with ipsilateral supraclavicular node involvement without distant metastasis.[11]

Multimodality treatment strategy is now the standard of care for LABC and neoadjuvant chemotherapy has been established worldwide. In our institute, we practice multimodality treatment for breast cancer since 1960. All LABC patients now receive uniform protocol with neoadjuvant concurrent chemoradiation followed by surgery and then completion of adjuvant chemotherapy and hormone therapy based on receptors. Studies had shown that the pathological response after neoadjuvant chemotherapy or chemoradiation protocol was high with better survival outcome. Earlier study from our institute and recent reports from United States had shown better outcomes in terms of survival benefit for patients who achieved pathological complete response after neoadjuvant chemoradiation treatment[7,8].

Apart from our institute there are very few reports on this uniform preoperative concurrent chemoradiation protocol for locally advanced breast cancer management. Hence we decided to analyse the pathological complete response rate and its impact on survival and to determine the clinicopathological factors associated with it.

3.MATERIALS AND METHODS

Previously untreated biopsy and cytology proven 831 stage III breast cancer patients treated at our institute between 2006 and 2008 with neoadjuvant concurrent chemoradiation were taken and 550 patients who had surgery after the neoadjuvant concurrent chemoradiation protocol were included in the study for analysis. All patients were clinically staged by IUCC- TNM 2002 classification system, Stage III (A, B, C).[12]

Study design: Retrospective study

3.1.Statistical analysis methods:

Frequency table described the various clinico-pathological factors, treatment response and outcomes. The survival difference was estimated by log-rank test and the statistical significance between the pCR and clinic-pathological factors by Pearson-Chi square test. Overall survival is defined as time from the date of diagnosis to date of death by any cause and disease free survival rate is the time from date of diagnosis to date of any loco-regional or distant recurrence or death.

3.2.Inclusion criteria :

1. Stage III breast cancer without prior treatment

3.3.Exclusion criteria:

1. Inflammatory breast cancer
2. Stage III breast cancer treated outside with chemotherapy or surgery (Excision biopsy or lumpectomy or simple mastectomy or modified radical mastectomy)
3. Not fit for chemoradiation

3.4.Management protocol:

The staging work-up included mammography, chest radiography, bone scan, ultrasonography of abdomen and pelvis, CT chest. All patients had biopsy or cytology proven diagnosis of breast carcinoma and cytology proven nodes if feasible. Receptor status and prognostic markers were also documented. Eligible patients received neoadjuvant concurrent chemoradiation according to the institute protocol, then are reassessed to undergo surgery and complete the remaining chemotherapy. Postoperative surgical specimen was processed according to the protocol and pathological response to neoadjuvant concurrent chemoradiation was assessed.

3.5.Treatment protocol:

All patients received neoadjuvant concurrent chemoradiation. Chemotherapy was administered every 3 weeks using one of the regimens- CMF/FEC/FAC/TE. Radiotherapy was delivered to breast and regional node along with chemotherapy after the completion of first chemotherapy cycle. Dose of radiation was 40 Gy in 180-200 cGy per fraction, 5 days/ week (Monday through Friday). Radiation was not usually delivered on the day of chemotherapy. A break in radiation occured if patient had treatment related toxicity. Patients were assessed once a week during chemoradiation, before each cycle of chemotherapy and at the end of chemoradiation for tumor response and toxicity. Total blood count was done twice weekly and whenever necessary. Hematological toxicity was recorded and normal tissue reactions were graded according to the RTOG toxicity criteria.

3.6.Radiotherapy:

Cobalt 60 beam was used to deliver radiation to the target areas which include involved breast, ipsilateral axilla and supraclavicular region. Internal mammary region was included in some patients. Treatment was delivered at a source skin distance of 80 cm.

3.7.Breast RT:

Patient was immobilised and arm maintained in abducted position. Radiation was delivered to breast using two tangential medial and lateral fields at an angle of 60 degrees and 120 degrees.

Upper border - inferior border of the clavicle

Medial border - midline

Lateral border - mid- axillary line

Inferior border - 2 cm below the infra mammary fold

Dose was prescribed at the center of the tumor, computing the dose from medial and lateral fields. Total dose was 40Gy in 20 fractions, 5 days per week.

3.8.SCL and Axillary RT: Combined field was used for SCL and axilla.

3.9.SCL radiation- Single direct field of size 15 x 10 cm (approximate) and the dose was calculated at 3 cm depth. Daily dose was 200cGy/day and total dose was 40Gy in 20 fractions, 5 days per week.

3.10.Axillary radiation - The dose contribution from the both tangential fields was measured at the midpoint of axilla and 3 cm from the tangential field's superior border. Posterior axillary boost was delivered with the patient in prone position, approximate field size is 8 x 10 cm and total dose was 40Gy in 20 fractions, 5 days per week. Field size and bolus requirement were individualised.

3.11.Internal mammary RT: Radiation to internal mammary region was delivered as indicated after surgery. It consists of a standard field size of 6x15 cm, extending from supra sternal angle up to xiphi-sternum and the field width was 6 cm extending 4 cm ipsilateral and 2cm across the midline.

3.12.Chemotherapy schedule:

Table 1.

REGIMEN	DRUGS	DOSE	ROUTE	DAYS
CMF	Cyclophosphomide	600 mg/m^2	Iv	Day 1
3 weekly	Methotrexate	50 mg/m^2	Iv	Day 1
	5-Fluro-Uracil	600 mg/m^2	Iv	Day 1
FAC	5-Fluro-Uracil	600 mg/m^2	Iv	Day 1
3 weekly	Adriamycin	40 mg/m^2	Iv	Day 1
	Cyclophosphomide	600 mg/m^2	Iv	Day 1
FEC-60	5-Fluro-Uracil	600 mg/m^2	Iv	Day 1
3 weekly	Epirubicin	60 mg/m^2	Iv	Day 1
	Cyclophosphomide	600 mg/m^2	Iv	Day 1
TE	Epirubicin	60 mg/m^2	Iv	Day 1
3 weekly	Paclitaxel	175 mg/m^2	Iv	Day 1

3.13.Hormonal therapy: All premenopausal women received Tamoxifen 10mg twice or 20 mg once daily and postmenopausal patients received Letrazole 2.5 mg once daily after completing the adjuvant chemotherapy based on the receptor status.

3.14.Surgery: After completion of concurrent chemoradiation patients were reassessed 4 weeks after the end of radiotherapy (stage IIIA, IIIB) for appropriate surgery (modified radical mastectomy) based on the skin condition. For stage IIIC LABC, patients were followed up regularly for 6 months after neoadjuvant chemoradiation. Those patients with no progression of disease and no metastasis were taken up for surgery. The remaining chemotherapy was administered after 3 to 4 weeks of surgery and radiotherapy to supraclavicular or internal mammary region as indicated. All premenopausal receptor positive patients were offered bilateral salpingo-opherectomy at the time of modified radical mastectomy. Surgical specimen was processed, prepared and assessed with consistent protocol by pathology department and reporting done. Pathological complete response (pCR) was defined as absence of any microscopic evidence of invasive tumor in the breast and axillary nodes.

3.15.Follow up: During follow-up, patient was followed every third month for first 3 years and then every six months for the 4^{th} and 5^{th} year, then annually. At each visit a detailed clinical history was taken and physical examination was done. Annual investigations with chest X-ray, ultrasonography abdomen and pelvis, contralateral breast mammography were done routinely but bone scan and CECT scan were done as warranted.

4.REVIEW OF LITERATURE

Breast cancer is a global problem and it contributes for a quarter of all cancers worldwide. The International Agency for Research on Cancer (IARC) the specialized cancer agency of the WHO had released the latest information on incidence, prevalence and mortality worldwide. GLOBOCAN 2012 the latest online database version of IARC‘s provides the recent estimate of global cancer burden across 184 countries worldwide for 28 types of cancer. Breast cancer is the most frequently diagnosed cancer among women in 140/184 countries. Since 2008 the incidence of breast cancer has increased by more than 20% and the new cases of breast cancer diagnosed in 2012 was 1.7 million (11.9%) worldwide. The incidence is highest in developed countries than the developing countries. In developed countries like Western Europe, North America, Australia, New Zealand the incidence is more than 90 per 1 lakh women annually, compared to 30 in east Africa and some Asian countries.[13]

Madras Metropolitan Tumor Registry (MMTR) at the Cancer Institute was established in 1982, the crude incidence rate (CIR) of breast cancer increased from 14.3 (1982) to 34.2 (2010). In India the incidence is high among the urban than the rural population, highest in Chennai followed by Mumbai, Delhi and Bangalore.[14]

Breast cancer is the leading cause of death among women worldwide in 2012[13]. In the west, death rate from breast cancer is declining despite increasing incidence. The annual reduction in mortality is 1.7% in North America since 1992 and 0.98% in the last decade among European Union. The decline in mortality is owing to the increase in early diagnosis and improved efficacy of adjuvant therapies. In developing countries and underserved areas of developed countries the scenario is different with high death rates, due to delay in diagnosis because of restricted health care access and difference in biology of the disease. WHO statistics reveals that the two components of early detection, namely education and screening programmes have reduced the mortality. For example in UK and US the reduction in breast cancer mortality was 12-13 lives per day.[13,15]

4.1.Breast cancer therapy evolution:

Breast cancer, one of the most common disease of women had captured the attention throughout the ages. The earliest known case of breast cancer was reported in 1600 BCE from the Edwin Smith Papyrus, Egypt.[16] Breast cancer therapy started with Leonides, a Greek physician who was credited with the first breast cancer operative treatment in the first century AD. Breast cancer surgery had a dramatic change in the

nineteenth century with the introduction of anaesthesia by William Morton in 1846 and the principle of antisepsis by Joseph Lister in 1867.

In the late 19th century, Sir William Halstead from Philadelphia, John Hopkins Hospital Medical School revolutionised the breast cancer treatment with his radical enbloc mastectomy which was unchallenged for 70 years, until modified by Patey in 1940. Halsteadian concept put forth in 1890 said that breast cancer was a localized disease to start with and then spread in a predictable and orderly manner to the regional nodal basin and then to systemic circulation.[17]

In twentieth century, Halsteadian radical mastectomy was challenged and the concept of lesser radical surgery, modified radical mastectomy was established with similar survival rates.

Since 1970 the contemporary trend of breast conservation surgery had evolved and validated through a series of carefully designed and well conducted controlled clinical trails through National Surgical Adjuvant Breast and Bowel Project (NSABP).

Bernard Fischer in 1980, put forth his theory that breast cancer was a systemic disease to start with and the treatment needed to be therefore directed to systemic therapy.[18]

Samuel Hellman in 1994, put forth his theory of “Spectrum Hypothesis” which states that breast cancer was a spectrum of diseases with one end of the spectrum being localized disease and the other end being systemic disease. Now, based on this hypothesis the breast cancer treatment targeted the local and the systemic components according to the stage of the disease.[19]

4.2.Locally advanced breast cancer:

LABC is a public health problem and poses challenges in the management worldwide. The incidence among the newly diagnosed cases were 40% to 60% in many developing and underserved developed countries.

Traditionally LABC included breast cancer of any size with skin and chest wall involvement[20]. The management of LABC had evolved in recent three decades. Historically surgery or radiotherapy alone had poor prognosis with high recurrence and death.

LABC includes

T3 (>5cm- TNM staging)

Any size with skin and chest wall involvement

Fixed or matted axillary nodes (N2)

Ipsilateral supraclavicular or subclavicular nodes (N3)

Haagensen and Stout inoperability critera includes[21]

1. Extensive skin edema (>50% skin involved)
2. Satellite skin nodules
3. Inflammatory type of cancer
4. Clinically involved Supra clavicular or Internal Mammary nodes
5. Edema of arms
6. Any **TWO** of the following grave signs:
    a. Skin ulcer
    b. Skin edema of limited extent (less than one-third of the skin over the breast involved)
    c. Tumor fixity to chest wall
    d. Axillary lymph nodes size 2.5 cm, or more, in transverse diameter and proved to contain metastases by biopsy
    e. Axillary lymph nodes fixity to the skin or the deep structures

Inoperable LABC treated with radiotherapy were associated with high complication rates with significant local control rate but the overall cure rate remained unchanged.

Combined modality treatment approach evolved in recent three decades, incorporating surgery, radiotherapy and systemic therapy and it

represented the standard of care for LABC. Multimodality treatment strategy included preoperative chemotherapy with theoretical advantages like early institution of systemic therapy, in vivo tumor response assessment, reduction in the size of primary tumor and lymph nodes. Despite the disadvantages like delay in local therapy, drug resistance, unreliable clinical staging for preoperative chemotherapy strategy, the clinical advantages of response assessment and possible breast conservative surgery were worth the use of neoadjuvant therapy.

Response to neoadjuvant chemotherapy both clinical and pathological rates were varying with chemotherapy regimens used.

In literature, the pathological response rate was reported to be 10-20% for anthracyclin based regimen and higher for taxane and trastuzumab based regimen. There was no optimal tool for clinical measurement of the tumor response. Imaging methods were more reliable than the clinical examination which were inaccurate and with inter-individual variations. Combination of both clinical and imaging methods was almost equivalent to the histopathological response. MRI, PET-CT and other newer modalities are under investigation, needs validation to incorporate in to the clinical practice.

Pathological complete response after neoadjuvant therapy was a prognostic factor which improved the long term survival.

Pathological complete response was a surrogate for survival but not prognostic for DFS and OS in all subtypes of breast cancer[22]. Recently conducted German and Global FDA meta-analysis had established that luminal A(HR+, grade 1or2) and luminal B(HR and Her2 positive) subtypes have less favourable outcome for patients with pCR. Luminal B(HR+, grade 3, Her2 negative), Her2 positive and triple negative subtypes had better outcomes on patients who achieved pCR than without pCR. Based on the meta-analysis information the three subtypes (Luminal B- HR+ grade 3, Her2 positive and triple negative) which were considered aggressive with poor prognosis had favourable prognosis if they achieved pCR.[23]

Various definitions for pCR have been proposed in the literature as follows

1.ypT<1a ypN+/-

2.ypTis ypN0+/-

3. ypT0 ypN0+/-

In FDA global meta-analysis the distribution varies

1.ypTis ypN0 - 5%

2.ypT0/is ypN+ - 4%

3.ypT0 ypN0 - 13%

German meta-analysis have established that patients with ypT0 ypN0- pCR had significant outcomes in terms of DFS and OS. FDA meta-analysis showed that between (ypTis ypN0) and (ypT0 ypTN0)-pCR, no relevant difference in event-free survival and OS. Both meta-analysis concluded that both (ypTis ypN0) and (ypT0 ypTN0) definitions are appropriate definitions for pCR in routine care and clinical trails[22,23].

Pathological complete response rate vary with different neoadjuvant therapy and depends on the receptor status. Generally pCR was higher with receptor negative tumor and unknown in receptor positive tumor. It was rare after neoadjuvant endocrine therapy and highest with combination of chemotherapy and trastuzumab.

Newer chemotherapy combinations like anthracyclin with taxanes (Epirubicin + paclitaxel or Doxorubicin + Docetaxal) yield overall response rate 80-95% and modestly higher clinical and pathological complete response when compared to older regimens. NSABP-27 trial had shown that sequential chemotherapy regimen with doxorubicin followed by taxanes (AC - Docetaxol) had higher overall response with significant pCR rates. Further it showed improvement in breast conservation and borderline survival benefits. Recent trials with targeted therapy in combination with neoadjuvant chemotherapy yielded higher

pCR upto 65%[24]. In the NOAH (NeoAdjuvant Herceptin) study trastuzumab combination increased the pCR rate by 20 % with significant improvement in event-free survival. Based on this trail the European Medical Agency had approved trastuzumab for neoadjuvant treatment[24]. GeparQuinto trial compared lapatinib combination with trastuzumab and chemotherapy which showed a trend towards low pCR rate[25]. Neosphere study showed higher pCR rate for docetaxel + trastuzumab + pertuzumab combination[26].

4.3.BCS in LABC:

BCS is feasible in a carefully selected subgroup of LABC patients after neoadjuvant therapy.

Selection criteria

1. Healing of skin ulceration
2. No skin or chest-wall fixation
3. Complete resolution of skin edema
4. Adequate reduction in tumor size
5. No collagen vascular disease
6. No extensive intramammary lymphatic invasion
7. Absent extensive suspicious microcalcifications
8. No evidence of multicentric tumor
9. Clear surgical margins

The outcomes in terms of local recurrence and 10 years overall survival in LABC patients undergoing BCS was equivalent to the BCS in early stage breast cancer. Skin involvement was not an absolute contraindication for BCS. Studies conducted by Shen et al 2004 and Guth et al 2005 had shown that BCS is feasible in LABC with noninflammatory skin involvement without affecting the local recurrence or survival rate and the outcomes are similar to the LABC patient without skin involvement[27,28]. Hence Guth et al suggested that non-inflammatory skin involvement LABC should be classified based on the tumor size and nodal status and T4- TNM should be revised. At our institute we do not offer BCS for stage III LABC.

4.4.Radiation role in LABC:

LABC is known for its high loco regional recurrence and systemic failure[29]. Internal mammary nodal involvement risk is up to 25 % in LABC[30]. Hence the need for loco regional control to target the occult tumor is achieved by the addition of radiotherapy. Radiation improves the local control and overall survival in stage III breast cancer. In stage IIIa, IIIb and IIIc with no gross residual tumor the local control rate is up to 90% with combined modality treatment[31].

4.5.Sequencing Multimodality treatment:

LABC is fraught with higher distant metastasis hence early systemic therapy (eg-neoadjuvant chemotherapy) is warranted to control systemic failure. The impact on local and distal control for chemotherapy and radiotherapy whether delivered simultaneously or sequentially remains to be established[32,33]. Most of the combined modality treatment strategy for inoperable LABC follows neoadjuvant chemotherapy – surgery – adjuvant chemotherapy - radiotherapy sequence[31].

Recent strategy is to complete all cycles of chemotherapy before surgery and to use two sequential neoadjuvant chemotherapy regimen[34,35]. This new strategy is based on the following observations.

1. Response monitoring and if no response or progression, a non-cross resistant chemotherapy agent is introduced.
2. The benefit of another non-cross resistant chemotherapy agent is irrespective of the response.

The benefits of this new strategy are

1. Increase in overall response and pCR rates

2. Reduce the drug resistance

The addition of targeted agent Trastuzumab with the neoadjuvant chemotherapy had shown better response and outcomes. It has increased the overall response rate, pCR rate and locoregional control.

The neoadjuvant concurrent chemoradiation has shown better local regional control and survival outcomes.

The demerits of concurrent chemoradiation given in the neoadjuvant settings are[33]

1.Slight increase in hematological toxicity

2.Acute radiation effects(skin toxicity)

3.Impairs cosmetic results of BCS

4.Cardiac toxicity in left side carcinoma breast

The combined modality treatment for LABC is a well tolerated modality with no increased surgical complications[36].

4.6.Survival effects:

Multimodality treatment benefits LABC in terms of survival. In stage III breast cancer trials have shown significant relapse free survival and overall survival benefit with multimodality treatment[37,38,39,40,41]. There are no randomized control trails comparing neoadjuvant with adjuvant chemotherapy in stage III breast cancer. But studies have shown equivalent survival benefit for stage III cancers whether chemotherapy delivered preoperatively or postoperatively[42,43,44,45,46,47].

4.7.Role of Pathologist - Specimen processing and reporting:

The pathologist play a vital role in the pathological assessment of response. With the advent of multimodality treatment, the pathological

examination of the specimen after neoadjuvant therapy is quite challenging. Clinical and radiological assessment under-estimate or over- estimate the residual tumor, hence the gold standard pathological examination is key in the assessment of pathological response.

Currently there are no standard criteria for classifying pCR, various systems are reported in the literature with different criteria to categorize the treatment response. Most of the system define pCR as absence of invasive cancer in the breast.

4.8.Criteria in various Systems - Categorizing treatment response

NSABP B-18[48]

pCR- No recognizable invasive tumor cells present

pPR - The presence of scattered individual or small clusters of tumor cells in a desmoplastic or hyaline stroma

pNR- Tumors not exhibiting the changes listed above

Miller-Payne System[49]

Grade 1 No change or some alteration to individual malignant cells, but no reduction in overall cellularity (pNR)

Grade 2 A minor loss of tumor cells, but overall cellularity still high; up to 30% loss (pPR)

Grade 3 Between an estimated 30% and 90% reduction in tumor cells (pPR)

Grade 4 A marked disappearance of tumor cells such that only small clusters or widely dispersed individual cells remain; 90% loss of tumor cells (almost pCR)

Grade 5 No malignant cells identifiable in sections from the site of the tumor; only vascular fibroelastotic stroma remains, often containing macrophages; however, ductal carcinoma in situ may be present (pCR)

Chevallier Method[50]

Class 1 Disappearance of all tumor (pCR)

Class 2 Presence of DCIS in the breast, no invasive carcinoma and negative lymph node (pCR)

Class 3 Presence of invasive carcinoma with stromal alteration (pPR)

Class 4 Few modifications of the tumoral appearance (pNR)

Sataloff Method[51]

Tumor

T-A Total or near total therapeutic effect (pCR)

T-B 50% therapeutic effect, but less than total or near total (pPR)

T-C 50% therapeutic effect, but effect evident (pPR)

T-D No therapeutic effect (pNR)

Nodes

N-A Evidence of therapeutic effect, no metastatic disease

N-B No nodal metastasis or therapeutic effect

N-C Evidence of therapeutic effect, but nodal metastasis present

N-D Viable metastatic disease, no therapeutic effect

RCB System[52]

RCB-0 No carcinoma in breast or lymph node (pCR)

RCB-I Partial response

RCB-II Partial response

RCB-III Chemoresistant

AJCC ‘‘y’’ Classification[53]

Category T Uses same criteria as before treatment

N Uses same criteria as before treatment

4.9.Sampling of tumor bed:

There is no established number of samples to be taken from the tumor bed, atleast one block per cm of the pretreatment tumor size is reasonable. If tumor residue is present, no additional sampling is required and if tumor residue is small entire area is submitted or if size more than 5 cm , atleast 5 sections are taken from the tumor residue. If no residue, number of additional samples to be done not yet established.

4.10.Microscopic appearance of tumor bed:

1. Area of hyalinized vascular stroma with stromal edema and fibroelastosis but no normal glandular ducts or lobules.
2. Stromal infiltration with foamy histiocytes, lymphocytes and hemosiderin pigments.
3. Area of necrosis leaving nodules of histiocytes and cholesterol clefts.

Cytological features mostly do not show changes except reduction in cellularity. DCIS shows no alteration after treatment. In difficult cases IHC correlation helpful in identifying the residual tumor and surgical margins by differentiating the epithelial cell(cytokeratin AE1/AE3/7) from the histiocytes(CD 68, CD 163).

4.11.Post-treatment nodal evaluation:

Lymphnode response are difficult to assess after neoadjuvant therapy since fibrotic and atrophic changes are extensive. Nodes are completely submitted and thin sections are taken for pathological assessment. Nodal response may be classified as positive nodes or negative nodes with evidence of treatment changes or negative nodes without treatment changes. Lymph node metastasis that show complete response to treatment are characterized by hyaline stromal scar, mucin pools, histiocyte aggregates with no viable tumor.

4.12.Reporting:

Breast Specimen

1. Presence and size of the tumor
2. Residual tumor size and extent
3. Residual tumor bed- average cancer cellularity
4. Residual tumor appearance and grade
5. Viability
6. Lymphovascular invasion
7. DCIS presence and extent
8. Margin status
9. Overall response comment

Lymph node status

1. Number
2. Size of the largest metastatic node
3. Extranodal extension
4. Number of metastatic node with evidence of treatment response
5. Number of nodes with evidence of treatment response but without tumor cells.

4.13.FIGURE

GROSS SPECIMEN

Figure 1.Mastectomy specimen showing grossly visible fibrotic tumor bed without residual tumor.

4.14. FIGURE

MICROSCOPY: pCR

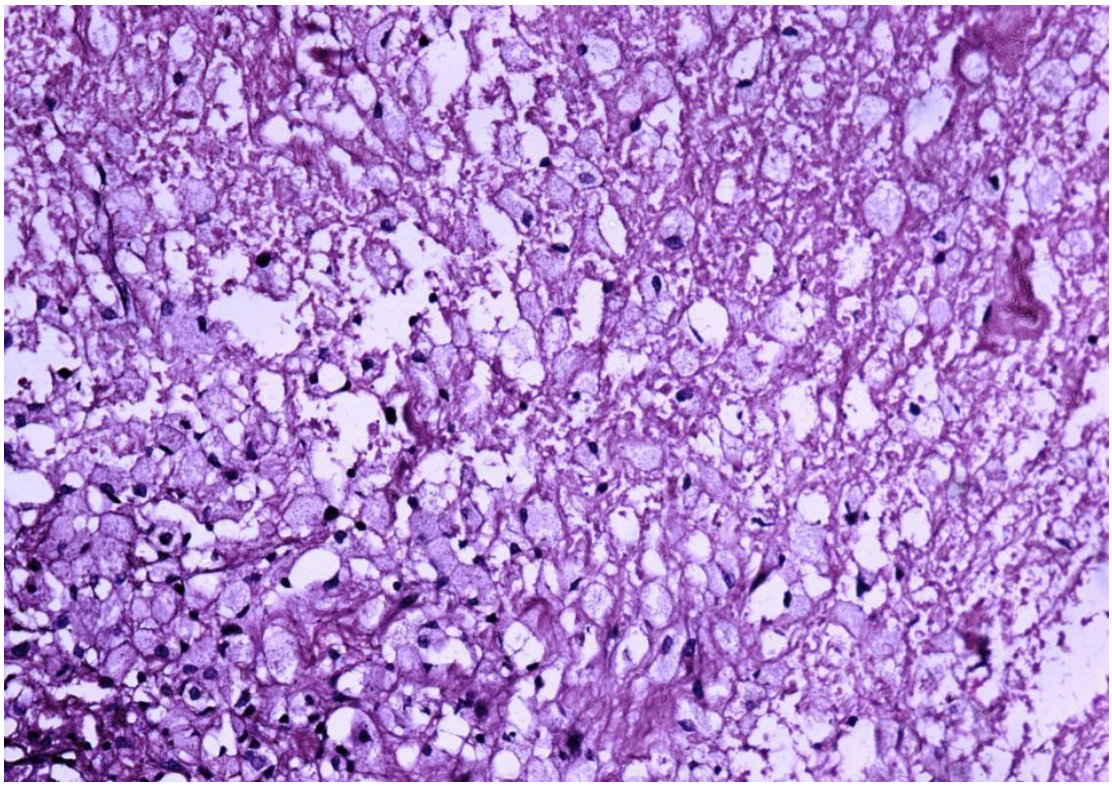


Figure 2. (Hematoxylin-eosin , magnification 20x) Complete pathological response showing histiocytes within the tumor bed.

5.RESULTS

5.1.AGE DISTRIBUTION:

In our study 91%(501) population were more than the 35 years of age and only 9%(49) were less than 35 years.

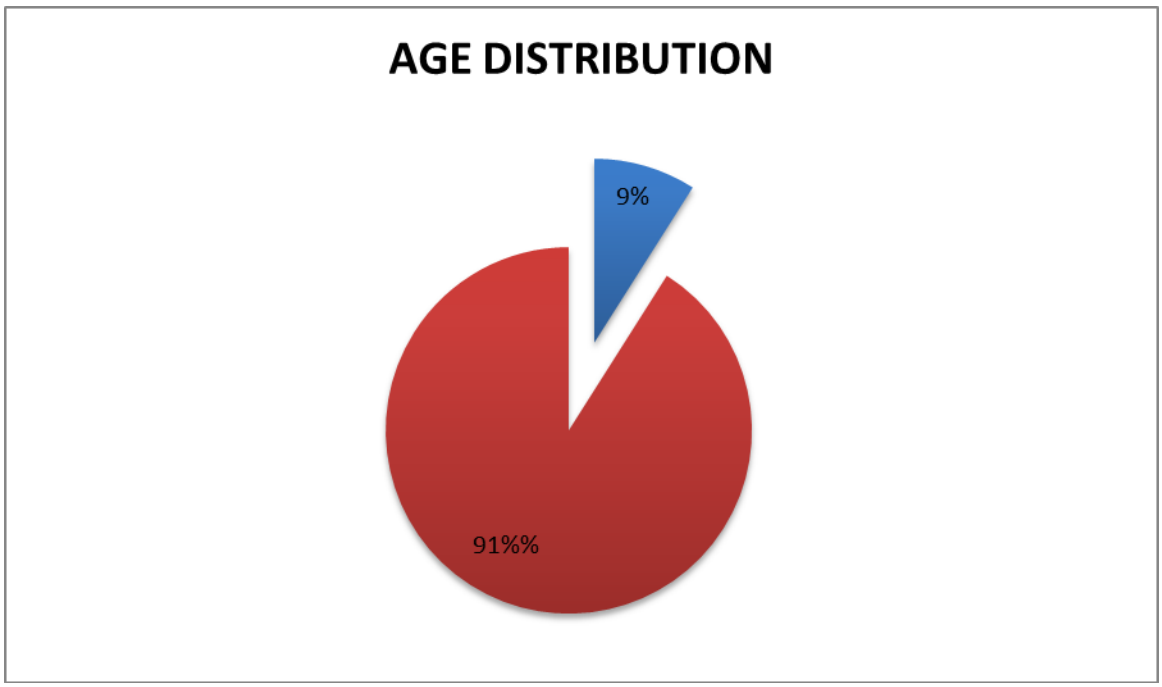


Figure 3. Pie chart representing the age distribution

Age > 35 years - 91 %

Age < 35 years - 9%

5.2.MENOPAUSAL STATUS:

Postmenopausal women were higher 56% (306) than the premenopausal 32% (176) and perimenopausal 12% (68) women.

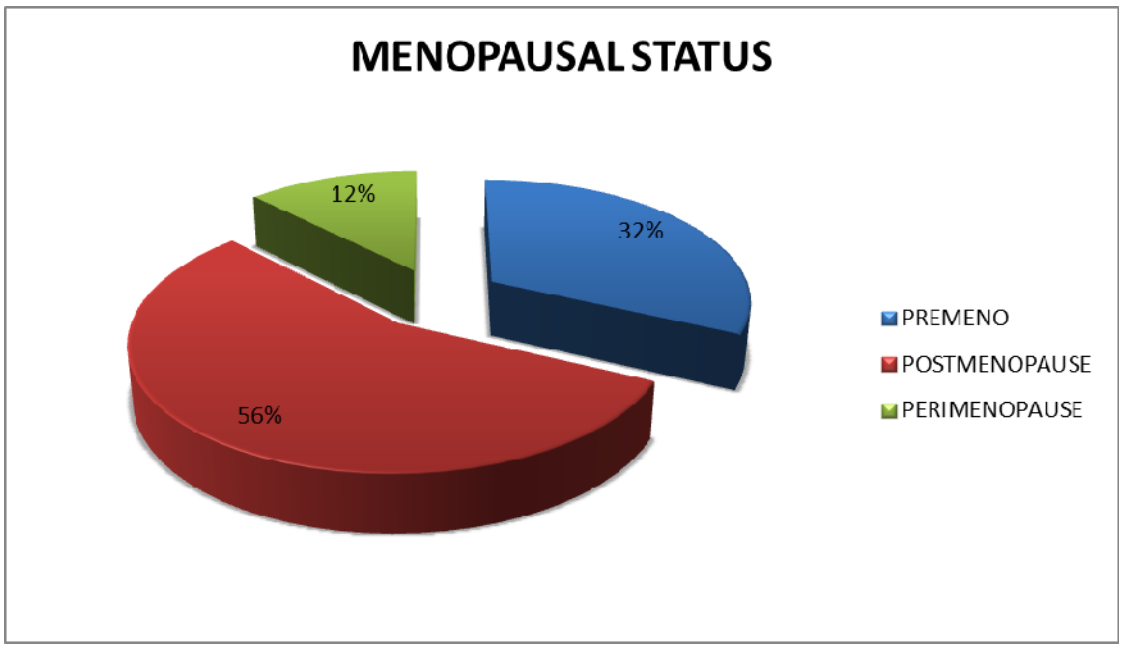


Figure3. Pie chart representing the menopausal status

Premenopausal - 32%

Perimenopausal - 12

Postmenopausal - 56%

5.3.STAGE DISTRIBUTON:

Among the study population 346 (63%) were stage IIIA, 190 (34.5%) were stage IIIB and 14(2.5%) were stage III C.

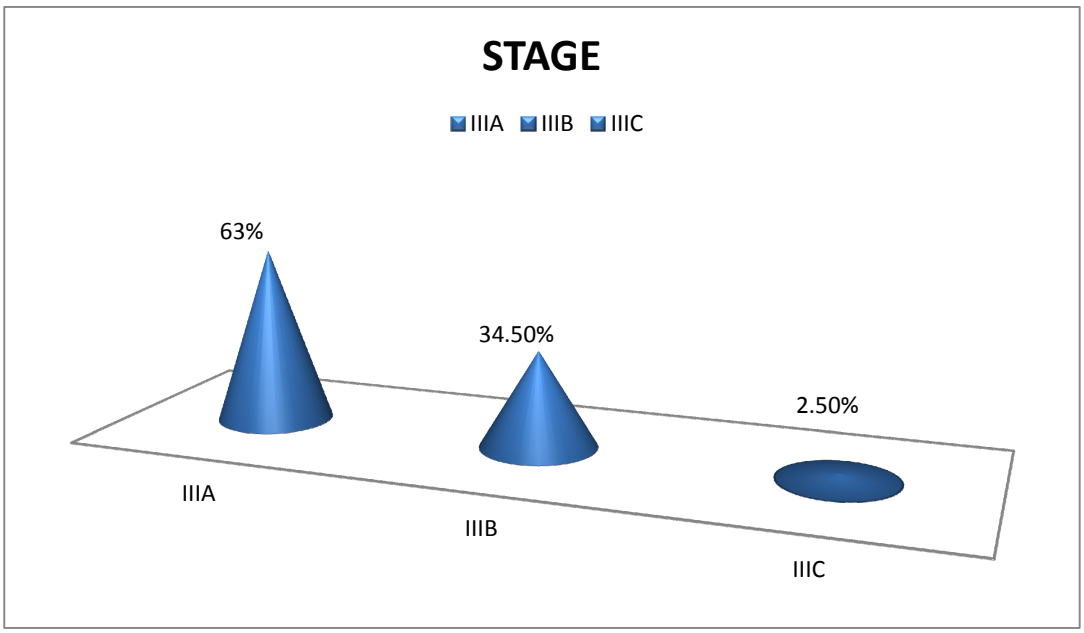


Figure 4. Column showing stage III breast cancer distribution.

5.4.HORMONAL RECEPTOR STATUS:

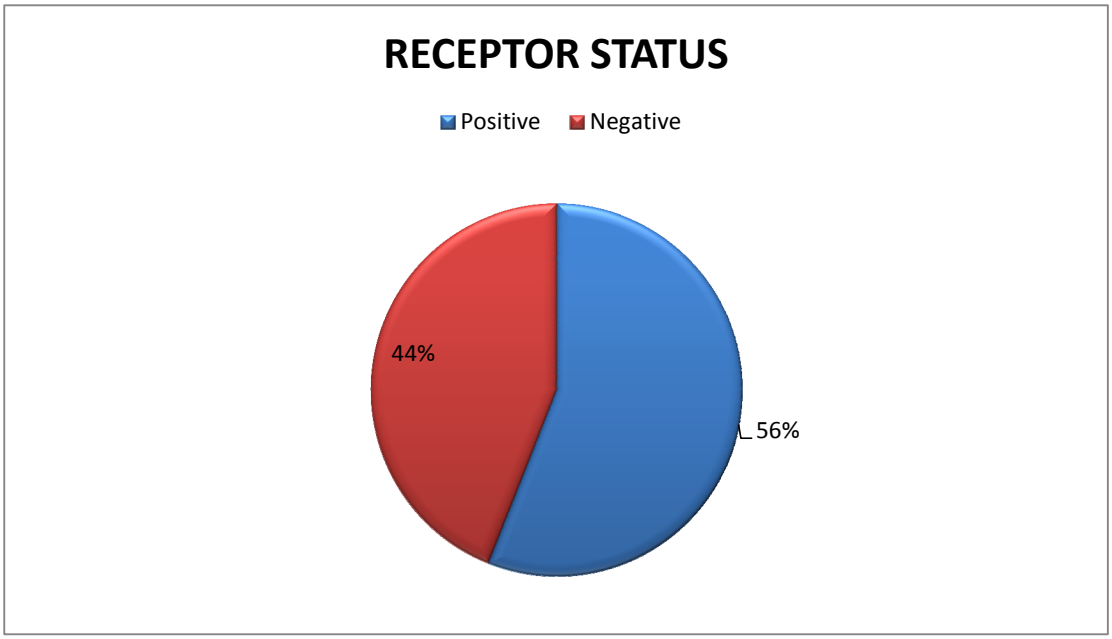


Figure 5. Pie Chart representing the receptor status distribution.

ER+ PR+ 223 (40%)

ER+ PR- 62 (11%),

ER- PR+ 25 (5%)

ER- PR- 240(44%)

5.5.HISTOPATHOLOGY TYPES:

The most common histology was infiltrating ductal carcinoma.

Infiltrating ductal Carcinoma - 67%

Infiltrating mammary Carcinoma - 3%

Infiltrating lobular Carcinoma - 1%

FNAC positive - 27%

Others - 2%

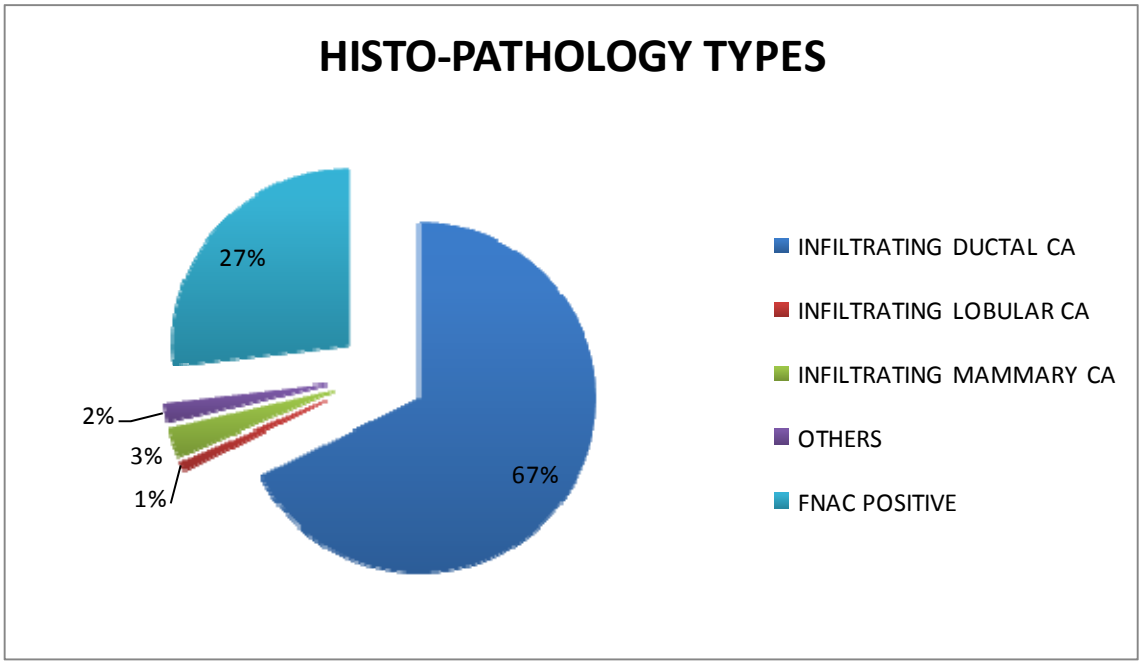


Figure 6. Pie chart representing the histopathological types

5.6.GRADE OF THE TUMOR:

327 (59%) patients had grade 3 and 217(40%) had grade 2 tumors.

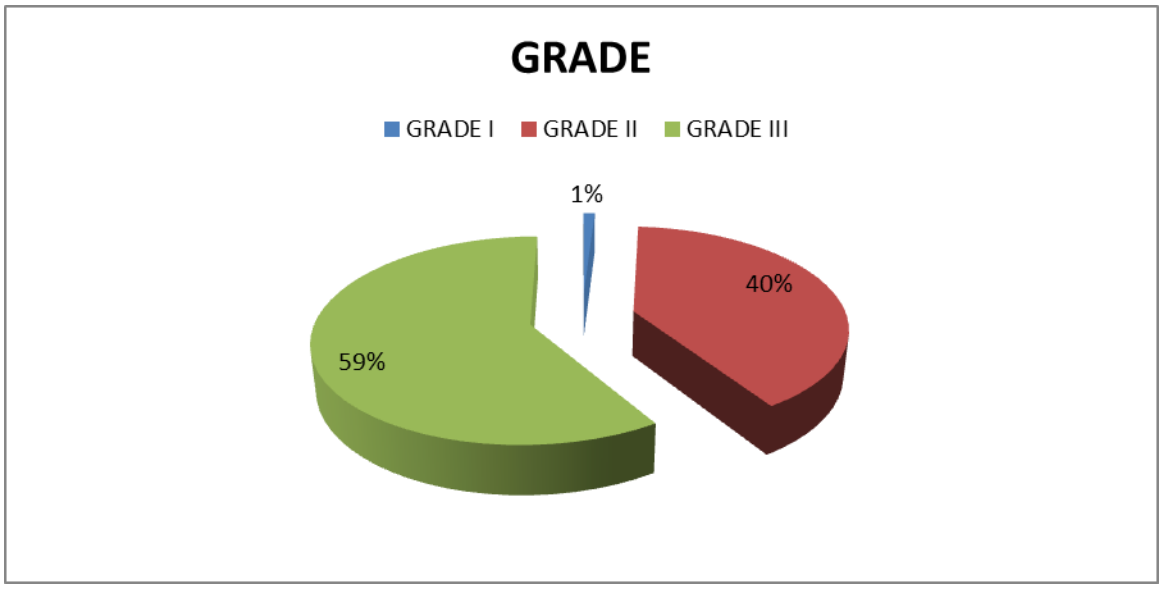


Figure 7. Pie Chart representing the tumor grade distribution.

Grade I – 1%

Grade II – 40%

Grade III – 59%

5.7.CHEMOTHERAPY REGIMEN:

FAC was the most common regimen used in 62% of patients.

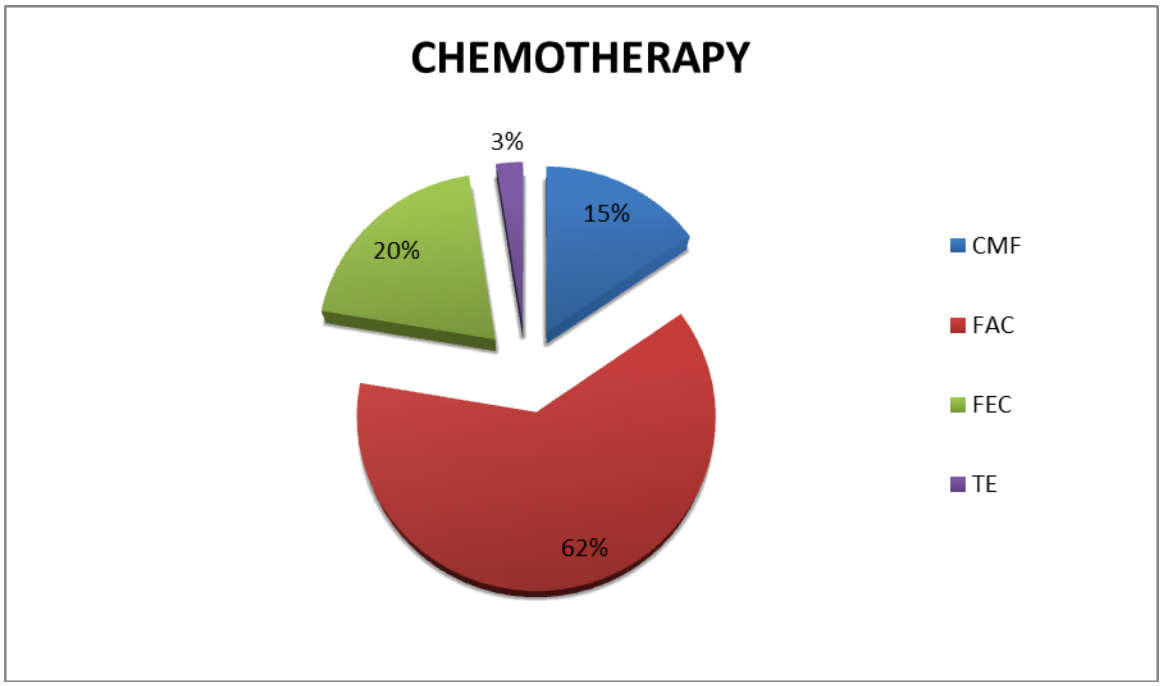


Figure 8. Pie Chart showing the different chemotherapy regimen used in the breast cancer treatment protocol.

FAC – 62%

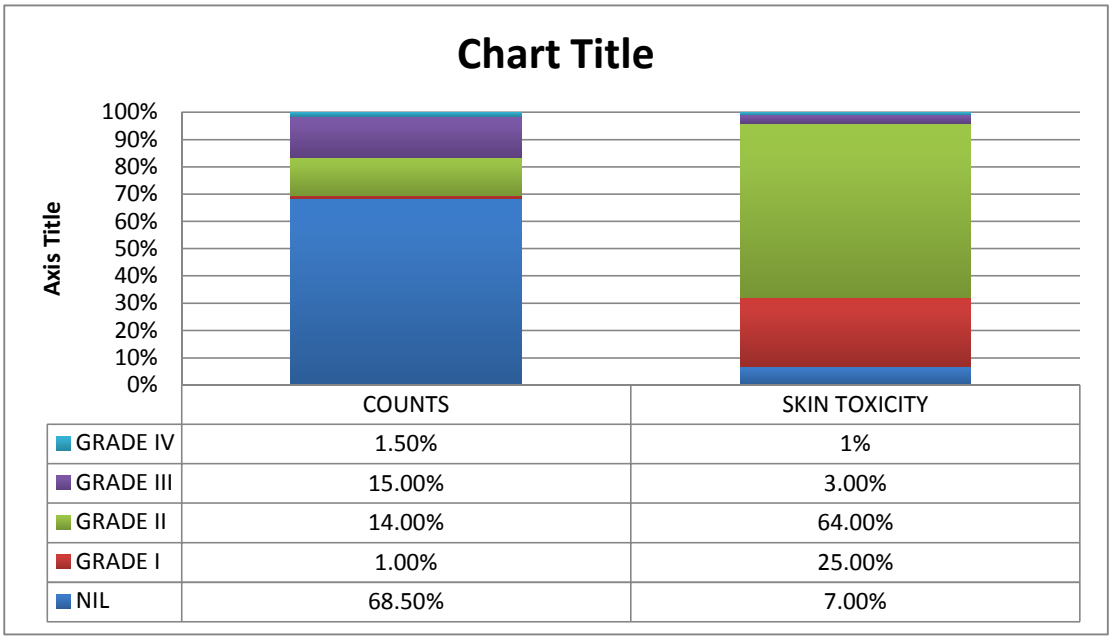
FEC - 20%

CMF- 15%

TE - 3%

5.8.TREATMENT TOXICITY:

Skin toxicity was the most commonly encountered treatment toxicity. Grade 2 dry skin desquamation was seen in 353 (64%) patients. Hematological toxicity with low counts - grade 2 in 14% and grade 3 in 15% were reported. Treatment delay during concurrent chemoradiation, more than 2 weeks were observed in 5 % due to skin and hematological toxicities. No treatment toxicity related death reported.



	COUNTS	SKIN TOXICITY
GRADE IV	1.50%	1%
GRADE III	15.00%	3.00%
GRADE II	14.00%	64.00%
GRADE I	1.00%	25.00%
NIL	68.50%	7.00%

Figure 9. Column representing the hematological and skin complications.

5.9.CLINICAL RESPONSE:

Overall response rate - 97%

Clinical complete response was achieved in 115 (21%) patients and partial response in 418 (76%) with 17 (3%) patients had stable disease.

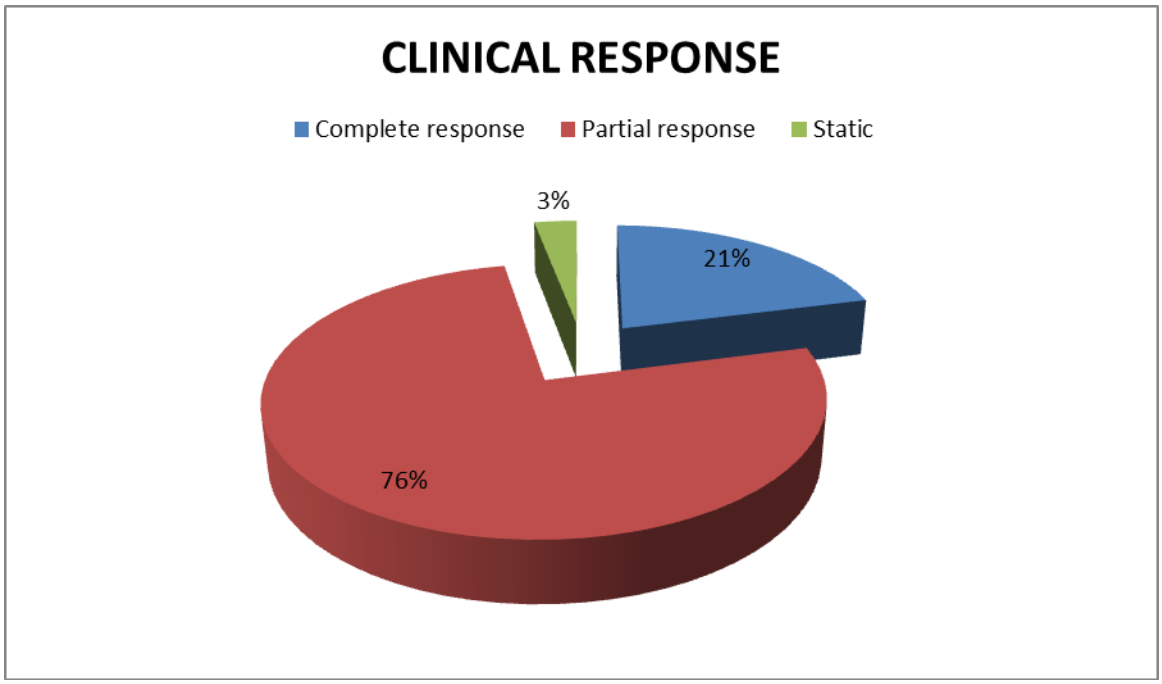


Figure 10. Pie Chart showing the distribution of clinical responses to the neoadjuvant concurrent chemoradiation protocol.

5.10.POST SURGICAL COMPLICATIONS:

No life threatening complications were encountered. Seroma was the most commonest morbidity reported in 109 (19.8%) patients which was managed conservatively. Eleven patients (2%) required skin grafting for necrosis of the wound. Wound infection rate was 5%. Upper limb lymphedema developed in fourteen patients (2.5%).

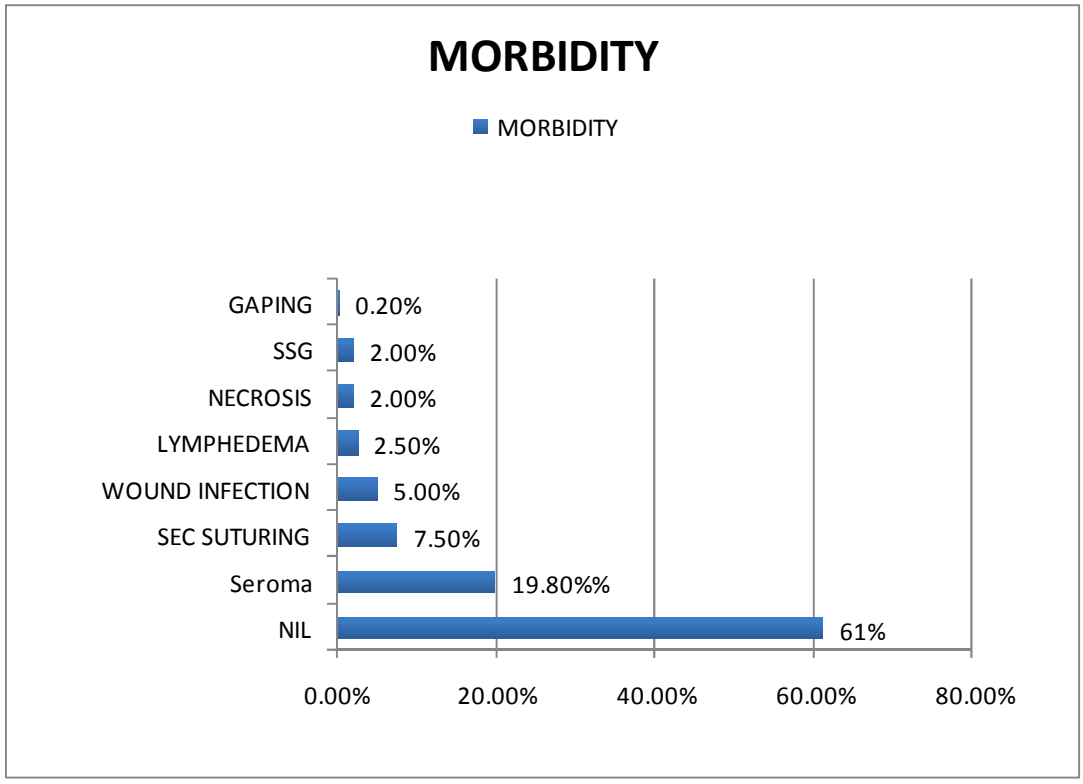


Figure 11. Bar Chart representing the surgery related morbidity.

5.11.PATHOLOGICAL RESPONSE:

Pathological complete response was achieved in 139 patients (25%).

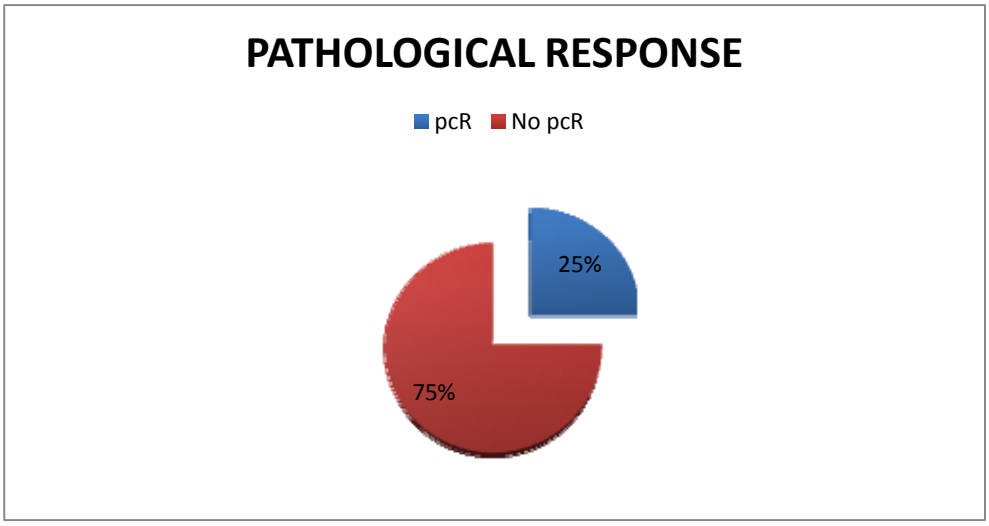


Figure12. Pie Chart representing the pathological response rate.

Table 2. DISTRIBUTION OF pCR & NON-pCR SUBSETS:

RESPONSE	NUMBERS	PERCENTAGE
ypT0 N0	139	25%
ypTis N0	9	1.5%
ypT+ N0	184	33.5%
ypT+ N+	193	35%
ypT0 N+	25	4.5%

5.12.HORMONE THERAPY:

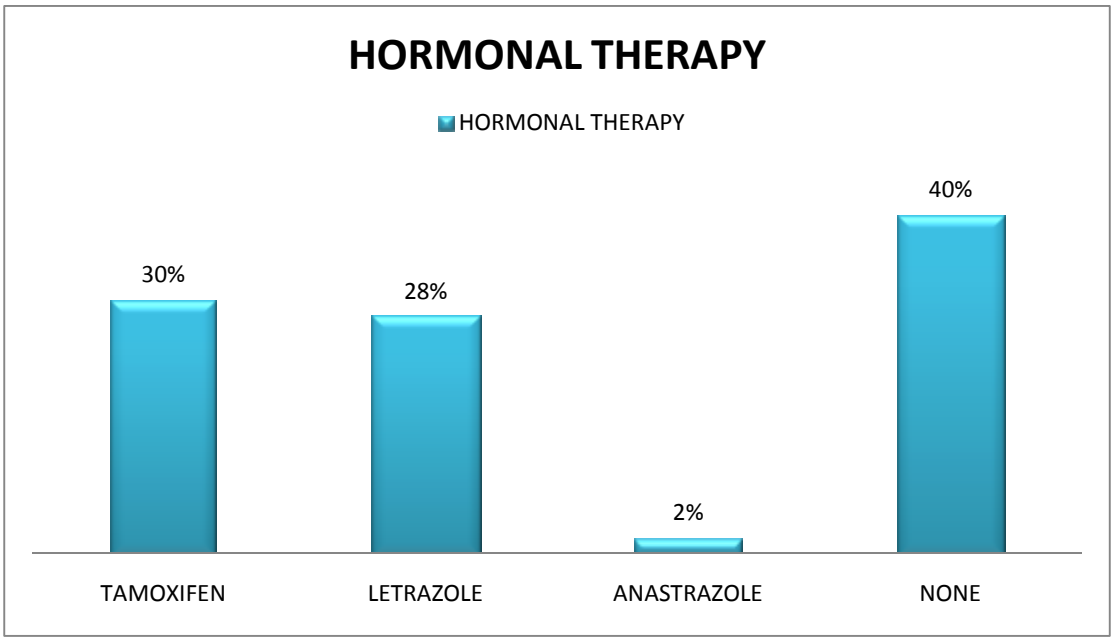
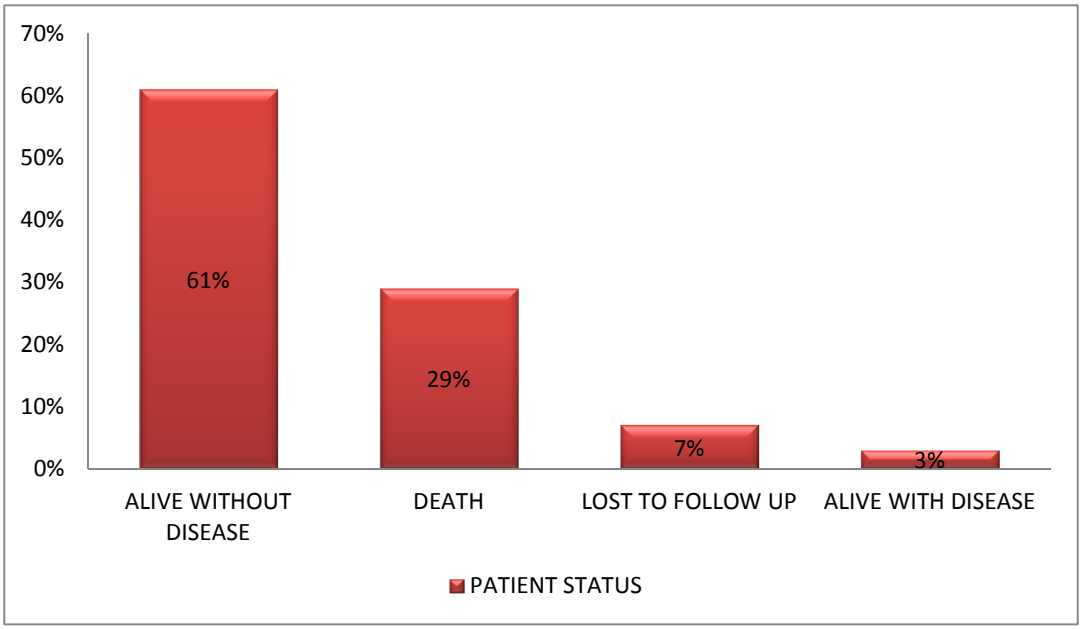


Figure 13. Column showing the percentage of various hormone agents used.

5.13.PATIENT STATUS AND RECURRENCE PATTERN:



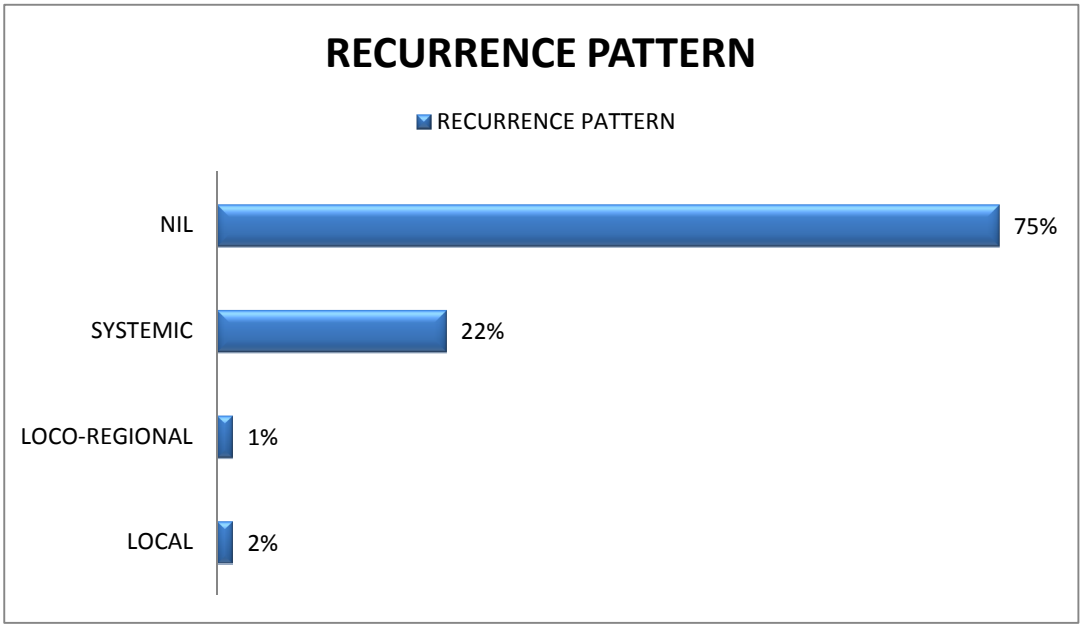


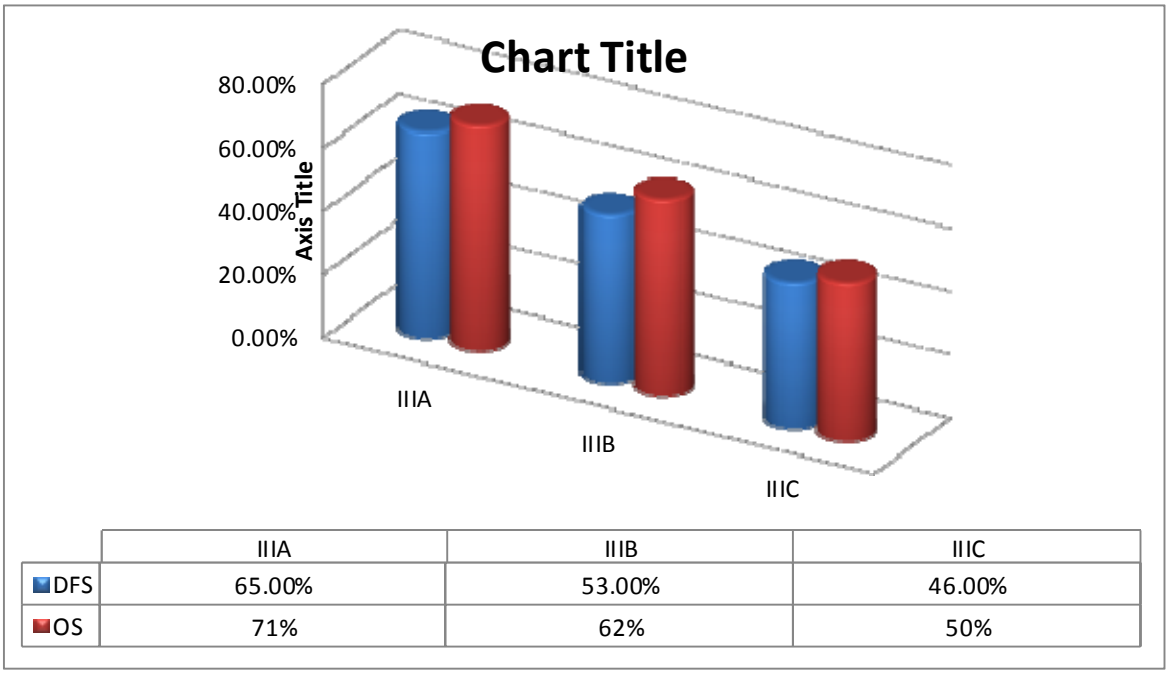
Figure 14. Column and Bar charts showing the patient status and recurrence pattern.

5.14. SURVIVAL - STAGE III

Stage IIIA – DFS 65% , OS 71%

Stage IIIB – DFS 53% , OS 62%

Stage IIIC – DFS 46%, OS 50%



	IIIA	IIIB	IIIC
DFS	65.00%	53.00%	46.00%
OS	71%	62%	50%

Figure 15. Bar chart diagram showing the survival- DFS and OS distribution in stage III breast cancer.

5.15.SURVIVAL CURVE – pCR

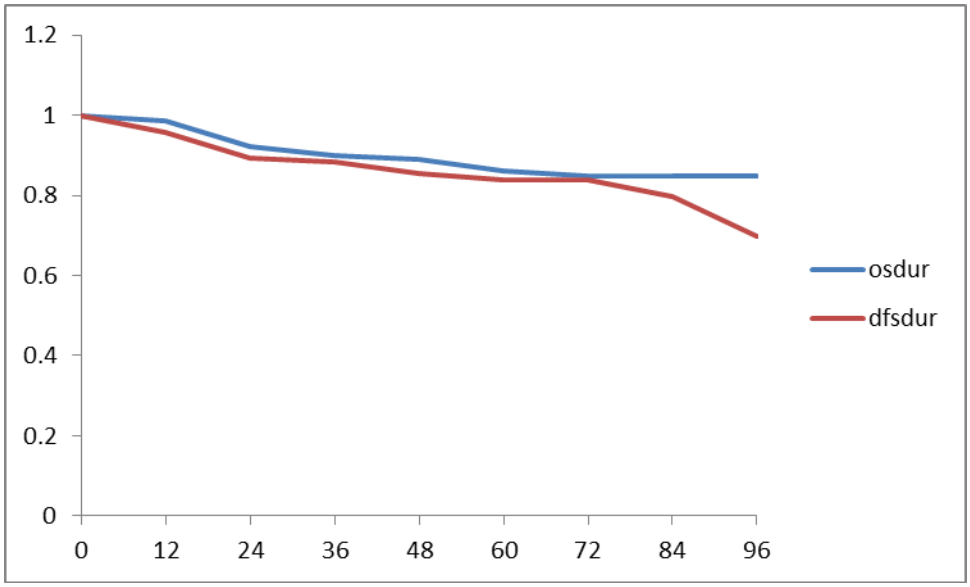


Figure 16. Survival curve representing the DFS and OS for pCR subsets.

5.16.SURVIVAL

The five year DFS and OS in our study were 69% and 72%. Patients who achieved pCR had significant survival advantage over the non-pCR groups in terms of DFS and OS.

OVERALL DFS

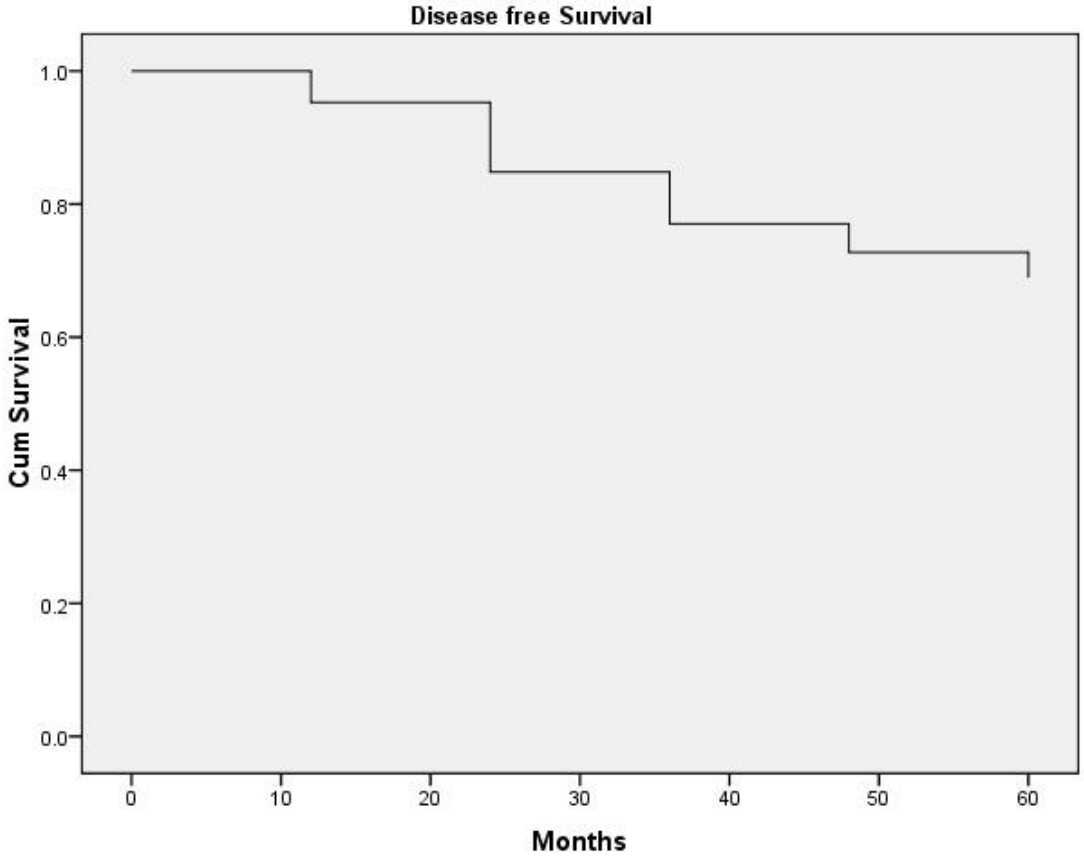


Figure 17. Survival curve DFS- 69%

OVERALL SURVIVAL

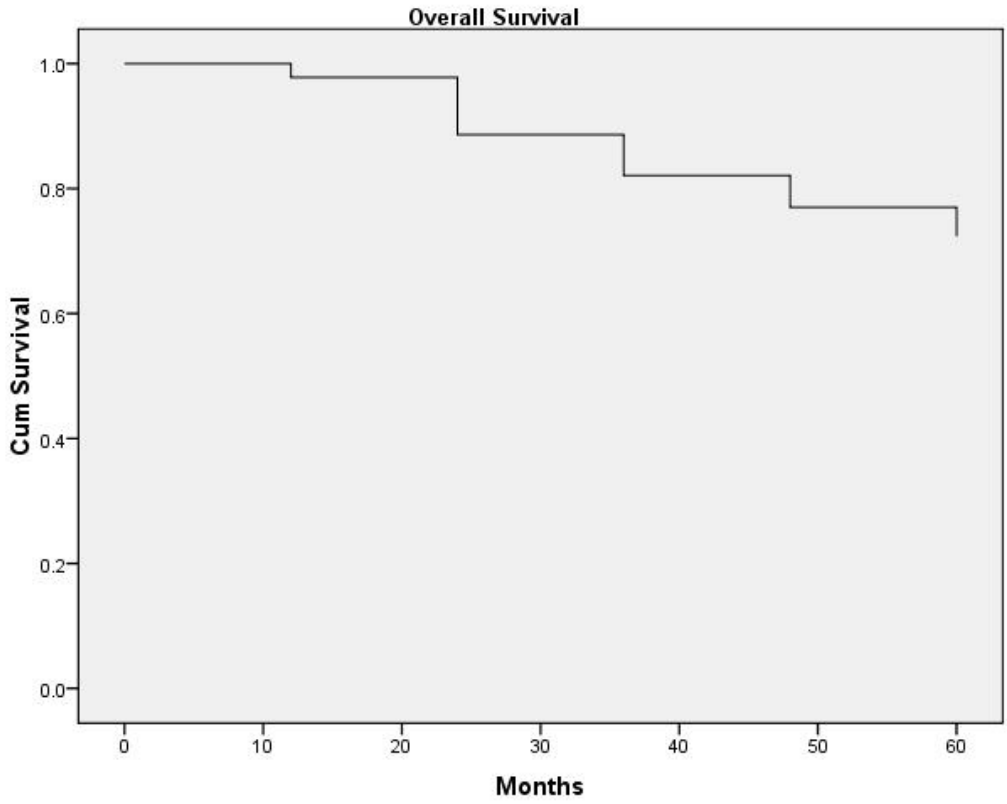


Figure 18. Survival curve OVERALL SURVIVAL- 72%

OVERALL SURVIVAL pCR vs NON-pCR:

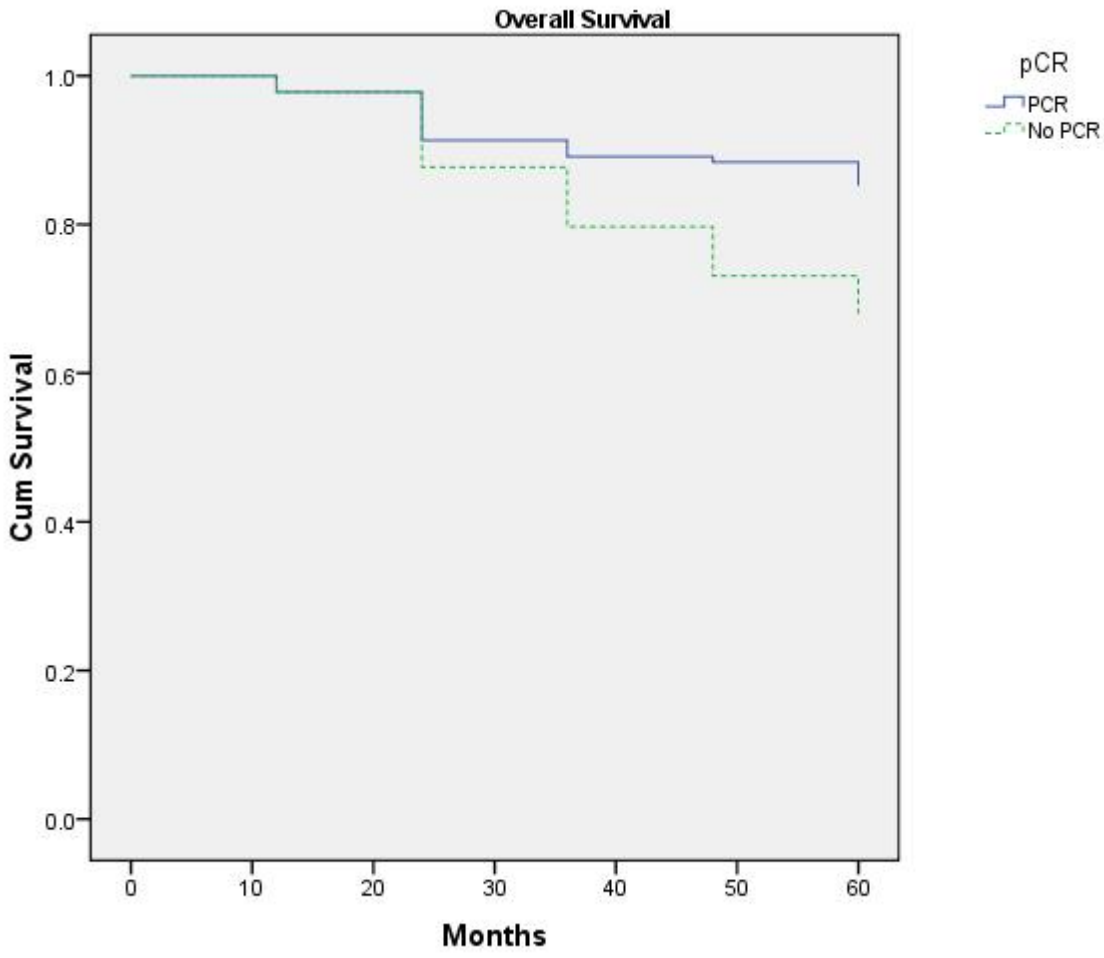


Figure 19. Survival curve

OS : pCR- 86% Non pCR- 68% p=0.015

DISEASE-FREE SURVIVAL pCR vs NON-pCR:

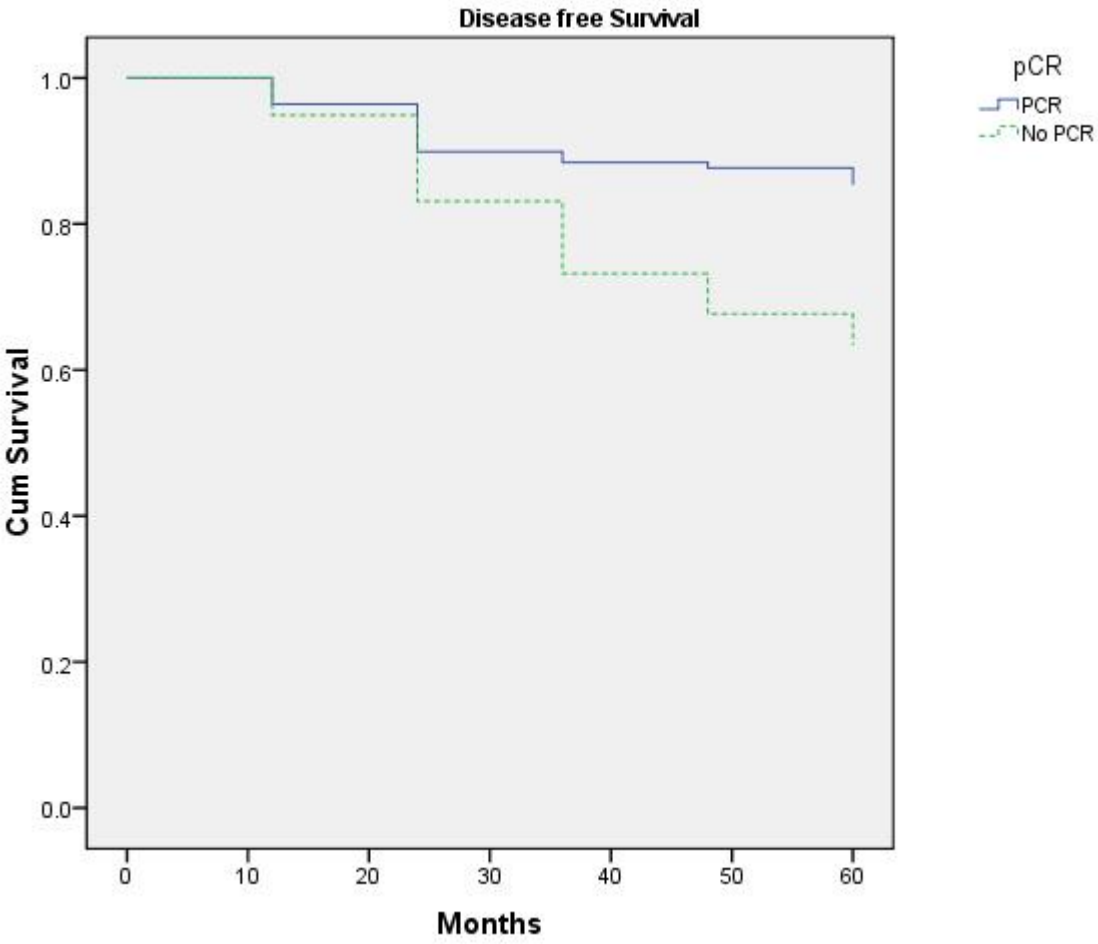


Figure 20.Survival curves

DFS: pCR- 84% Non pCR- 63% p=0.031

6.DISCUSSION

The majority of patients with breast cancer are diagnosed with locally advanced stage in our country with poor treatment outcomes. With the introduction of multimodality treatment the outcomes have improved for these patients. In our study the incidence of stage III LABC was 39% and most of them are postmenopausal (56%) women. The early onset proposition was 9%.

Neoadjuvant concurrent chemoradiation is a feasible option with good tolerance and improved outcome in high risk LABC patients.

In our institute multimodality treatment is in practice since 1960 and preoperative radiation for LABC was given between 1960 and 1969 to down stage the tumor for surgery. This modality had excellent loco-regional control, but patients succumbed to systemic failure. With the advent of adjuvant chemotherapy worldwide in 1970, we in our institute started using neoadjuvant concurrent chemoradiation for LABC ensuring loco-regional and systemic control of the disease with improved outcomes.

Objectives of combining chemotherapy and radiation are

1. Early target of micrometastasis
2. Synergistic action in downstaging the primary tumor and nodes

Between 2006 and 2008 at our institute, we have treated 831 patients with stage III breast cancer. Among them 550(66%) patients who received uniform concurrent chemoradiation protocol and completed the treatment were included for analysis. The rest of 281(34%) patients were excluded for the following reasons,

- 4.5% had received treatment outside (chemotherapy, surgery-lumpectomy, modified radical mastectomy)
- 5% did not receive protocol preoperative concurrent chemoradiation
- 3% defaulted before starting or during the concurrent chemoradiation treatment
- 6% defaulted after completing the chemoradiation protocol
- 7% declined surgery after completing the chemoradiation protocol
- 7% had progression and not completed the treatment

In our study 550 patients received the protocol concurrent chemoradiation with 40 Gy total dose radiation to breast, axilla and /or supraclavicular region and one of the chemotherapy regimen. The most common regimen combined with radiation was FAC (62%) and other regimens were FEC-20%, CMF-15%, TE-3%. FAC and FEC-60 was most commonly used with concurrent radiation so as to keep the toxicity less. The concurrent chemoradiation treatment protocol was well tolerated. Skin toxicity was the most common reported toxicity with grade I-25%, grade II- 64%, grade III-3% grade IV-1% (RTOG criteria). Hematological toxicity in terms of low counts (Abridged common toxicity criteria) grade I- 1%, grade II- 14%, grade III- 15% and grade IV- 1.5% were reported and febrile neutropenia were managed appropriately. Treatment delay during concurrent chemoradiation, more than 2 weeks were observed in 5% of patients in our study. Skin and hematological toxicities were manageable without any mortality.

Formenti et al studied 44 patients and reported that skin desquamation was the most common toxicity during or after concurrent RT/paclitaxel protocol. Twenty patients (20/44 - 45%) developed moist desquamation. Delay in surgery was reported due to skin toxicity[8].

Bapsi chakravarthy et al studied 38 patients with chemoradiation protocol with paclitaxel/RT. 87% completed the protocol without delay or dose reduction during treatment and one patient had grade 3& 4 toxicity[54].

Following completion of chemoradiation, skin assessment was done after 4 weeks and then planned for surgery followed by completion of the adjuvant chemotherapy. The median treatment duration in our study was 6 months.

In our study all 550 patients had modified radical mastectomy and no mortality was reported. The most common surgical complication was seroma (20%). Other complications were wound infection, minimal wound gaping with no intervention, marginal necrosis, secondary suturing, skin grafting for necrosis and lymphodema.

Overall response rate in our study was 97% which includes clinical complete response 21% (115/550), partial response 76%(418/550) and stable disease 3% (117/550). Formenti et al from University of Southern California Los Angeles USA studied 44 patients with neoadjuvant chemoradiation with paclitaxel and reported 91% overall response with complete response in 11%(5/44), partial response 80%(35/44) and stable disease in 9%(4/44)[8].

Pathological complete response in both breast and axilla was achieved in 25 % (139/550) in our study. Pathological complete response reported in various preoperative chemoradiation protocol were 12 to 39 % and all studies were limited by their small samples. Formenti et al treated 44 patients and achieved 34%(15/44) pCR, Sauter et al studied 20 patients with pCR 12%(4/20), Bapsi chakravarthy et al reported pCR rate of 34%(13/38) with sample size of 38 patients and Serin et al studied 28 patients and achieved 39% pCR(11/28)[8,9,54,55].

In our study the incidence of pathological complete response showed statistical significant association with the receptor status ER (p=0.001), PR (p=0.001), grade of the tumor (p=0.001) and chemotherapy regimen (p=0.009). Other patient and tumor related factors like age of the patient (p=0.213), menopausal status (p=0.163), histology type of the tumor (p=0.617), clinical stage (p=0.308), clinical tumor status (p=0.092) and clinical nodal status (p=0.840) had no statistical correlation with pCR. The total number of chemotherapy cycles delivered before surgery also had no impact on achievement of pCR (p=0.323).

Several studies have shown significant association between pCR and long-term survival outcomes. Pathological complete response may represent a surrogate for disease-free and overall survival rate. Neoadjuvant chemotherapy had been established as conventional and standard of care for LABC with variable pathological response rate. The 5 years disease free and overall survival were 36% to 61% and 49% to 69% respectively reported by several trials for neoadjuvant chemotherapy protocol[56,57,58,59,60]. Whether pCR and its survival outcomes achieved after neoadjuvant chemotherapy or concurrent chemoradiation protocol is superior, need to be addressed by randomized trails.

Adams et al in 2010 from New York University School of Medicine reported that higher pCR rates correlated with superior five years disease free and overall survival rate for preoperative concurrent chemoradiation protocol with paclitaxel[61].

In our study there is a statistically significant association between pCR and survival outcomes. The five year disease free and overall survival for all 550 treated patients were 69% and 72 %. Those who achieved pCR, the five year DFS-84% and OS-86% was statistically significant when compared with non-pCR group five year DFS-63% and OS-68%. (DFS $p = 0.031$ and OS $p = 0.015$).

7.CONCLUSION

Multimodality treatment strategy has been established as a standard of care for locally advanced breast cancer. Neoadjuvant chemotherapy protocol was standardised as the conventional approach worldwide with improved long term outcomes.

At our institute, we are practicing multimodality approach for breast cancer since 1960. Our treatment policy of preoperative concurrent chemoradiation was a uniform protocol.It had consistently showed improved outcomes for locally advanced breast cancer, from the present study and previous published studies from our institute.

All 550 patients treated with this protocol tolerated the treatment well without any treatment related mortality. The morbidities reported in our study were manageable.

The pathological complete response achieved in our study was 25% comparable with 12% to 39 % reported in the literature for neoadjuvant concurrent chemoradiation protocol, considering the fact that majority in our study received anthracyclin containing regimen without taxanes.

The clinicopathological and treatment factor like receptor status ER/PR, grade of the tumor and the chemotherapy regimen had a

statistically significant association with the pathological response rate. The number of chemotherapy cycles received before surgery had no statistical impact on the pCR.

The five year DFS and OS was 69% and 72% respectively which was a better survival outcome for stage III breast cancer compared to world standards. Also the local and loco regional failure rates are lower in our study group than that reported in the literature.

Complete pathological response is a reliable surrogate marker of survival outcomes. Locally advanced breast cancer patients who are already at high risk for local and distant failure can have favourable long term survival outcomes by achieving pCR with the multimodality treatment approach.

8.ANNEXURE

PROFORMA

NAME: AGE: SEX:

UHID NO: CI.NO:

POST/ PREMENOPAUSAL PARITY: 1/2/3/4/5/6/7

AGE AT FCB:

PREVIOUS BREAST BIOPSY: Y /N

CLINICAL STAGE: cTNM

FAMILY HISTORY: DEGREE 1 / 2 / 3

METHOD OF DIAGNOSIS: FNAC / TRUCT BIOPSY / EXCISION BIOPSY / INCISION BIOPSY

HPE REPORT: IDC / ILC/ IMC/ METAPLASTIC/ OTHERS

GRADE : I / II / III NG : LOW / INT / HIGH

RECEPTORS: ER: + / - PR + / - CERB2 + 1 / 2 / 3

P53 CATEPSIN (CYTOLOGY / HPE)

METASTATIC WORK UP:

CXR: NORMAL/ABNORMAL FINDINGS IF ANY

BONE SCAN: NORMAL/ABNORMAL FINDINGS

USG LIVER:

USG PELVIS:

OTHERS: MAMMOGRAM CT CHEST-

PERFORMANCE STATUS- 1 /2

TREATMENT DETAILS:

DATE OF INITIATION OF TREATMENT:

NEOADJUVANT TREATMENT: (PROTOCOL)

CONCURRENT RT+CT / INDUCTION CT – RT

CHEMOTHERAPY:

TYPE AND DOSE: CMF / FAC / FEC / AC / TE

NO OF CYCLES:

BEFORE RT:

DURING RT:

AFTER RT :TOXICITY: FEVER / LOW COUNTS-

GRADE 1 /2/3 DELAY-

RADIATION:

TECHNIQUE:

SITE: RT / LT – BREAST / AXILLA / SCL / IMR

DOSE:

DATE:

ANY DELAY / INTERRUPTION:

SKIN TOXICITY: GRADE I / II / III / IV

ASSESSMENT OF CLINICAL RESPONSE:

COMPLETE / PARTIAL / STABLE / PROGRESSION

SURGERY:

DATE OF SURGERY:

TYPE OF SURGERY: MRM + AXILLA LEVEL 1,2,3

COMPLICATIONS: SEROMA / GAPPING / NECROSIS/ RESTRICTED ARM MOVEMENTS/ LYMPHEDEMA

HPE:

TUMOUR	NODES
RESIDUE (YES / NO)	TOTAL -
SITE – UOQ/UIQ/LOQ/LIQ/CS	LEVEL I
SIZE: _____	LEVEL II
MARGIN_____	LEVEL III
LVSI - Y / N SKIN/ NIPPLE – Y /N	PNS

PCR: Y / N PATHOLOGICAL STAGE – p T N

ADJUVANT TREATMENT:

CHEMOTHERAPY- CMF/FAC/FEC/TE/AC

RADIOTHERAPY – SCL / IMR

HORMONE THERAPY: TAMOXIFEN / LETRAZOLE

RECURRENCE: IF ANY

LOCAL / REGIONAL / SYSTEMIC / LOCAL AND REGIONAL / LOCAL AND SYSTEMIC /

REGIONAL AND SYSTEMIC

DATE OF DIAGNOSIS OF RECURRENCE:

CONFIRMATION OF RECURRENCE:

CYTOLOGY / BIOPSY / IMAGING / NONE

TREATMENT OFFERED:

SURGERY:

CHEMOTHERAPY

RADIATION

HORMONE THERAPY

SUPPORTIVE CARE ONLY

PROGRESSION IF ANY AND TREATMENT OFFERED:

LAST VISIT AT OPD:

STATUS AT FOLLOW UP:

DISEASE FREE/ ALIVE WITH DISEASE / DIED OF DISEASE/ DIED OF OTHER REASONS/ LOST TO FOLLOW UP

DFS:

OVERALL SURVIVAL:

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